RING THE BELLS THAT STILL CAN RING
FORGET YOUR PERFECT OFFERING
THERE IS A CRACK, A CRACK IN EVERYTHING
THAT'S HOW THE LIGHT GETS IN.

- LEONARD COHEN

UNIVERSITY OF ALBERTA

NUTRITIONAL SUPPLEMENTATION IN ADVANCED CANCER PATIENTS

by

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ABSTRACT

Interventions for weight loss in cancer patients focus on oral nutritional supplementation; their benefit may be limited by compensating decreases in meal intakes. The effect of a palatable, protein dense nutritional supplement in improving macronutrient intakes of advanced cancer patients was investigated. Twelve subjects consumed the supplement twice per day between meals, for 7 days. Dietary intakes, 24-hour urinary urea nitrogen, and plasma phospholipids were measured before and after supplementation. Two distinct behaviours in response to energy intake at meals during supplementation were seen. In six subjects, a large reduction in meal intakes, (551 SD 368 kcal/d, P=0.015) negated supplement intake. The other six subjects did not alter their meal intakes, and increased total intake by 717 SD 331 kcal/d (P=0.001). The inability to discriminate patients likely to respond with compensatory behaviours is an impediment to the rational application of dietary supplements.

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I WOULD LIKE TO DEDICATE THIS WORK TO THE MEMORY OF MY GRANDMOTHER,

SYLVIA CHECHOVICH.

YOUR LOVE AND ENCOURAGEMENT IS EVERLASTING.

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List of Abbreviations

µg	microgram
AIDS	acquired immune deficiency syndrome
AA	amino acid
BF	butter fat
BMI	body mass index
BV	biological value
BW	body weight
CCK	cholecystokinin
cm	centimetre(s)
Cys	cysteine
d	day
DHA	docosahexaenoic acid
EPA	eicosapentaenoic acid
ESAS	Edmonton symptom assessment scale
fl oz	fluid ounce
g	gram(s)
GIP	glucose-dependent insulinotropic polypeptide
GLP	glucagon-like peptide
Ile	isoleucine
kcal	kilocalorie
kg	kilogram
Leu	leucine

m^2	meter(s) squared
Met	methionine
mg	milligram(s)
ml	millilitre(s)
MUFA	monounsaturated fatty acid(s)
NPU	net protein utilization
oz	ounce
PDCAAS	protein digestibility corrected amino acid score
PER	protein efficiency ratio
PG-SGA	patient-generated subjective global assessment
Phe	phenylalanine
PL	phospholipid
PUFA	polyunsaturated fatty acids(s)
SD	standard deviation
SFA	saturated fatty acid(s)
Trp	tryptophan
Tyr	tyrosine
UUN	urinary urea nitrogen
Val	valine

CHAPTER ONE

1.0 BACKGROUND AND LITERATURE REVIEW

1.1 INTRODUCTION

Cancer is a general term for a host of more than one hundred diseases characterized by uncontrolled and abnormal cell growth. The National Cancer Institute of Canada estimated there to be approximately 149,000 new cancer diagnoses (13,001 in Alberta) and more than 69,000 cancer-related deaths (5,500 in Alberta) in 2005 (Canadian Cancer Society/National Cancer Institute of Canada, 2005). Three types of cancers account for at least 50% of all new cases: in men prostate, lung, and colorectal, and in women breast, lung, and colorectal (Canadian Cancer Society/National Cancer Institute of Canada, 2005). Cancer is considered a disease of the elderly with the average age for a new cancer diagnosis occurring between 60 and 69 years of age (Canadian Cancer Society/National Cancer Institute of Canada, 2005).

After a cancer diagnosis, treatment options are explored and may include surgery, chemotherapy, radiation, or a combination of two or three treatment modalities. A cancer diagnosis made in the early stages of the disease trajectory is pursued with the intent to cure. However, cancer diagnoses are often made in the later stages of the disease, and it is at this point when treatment options are limited and aimed toward prolonging life and the of palliation symptoms. Unfortunately, one out of every four Canadians will die from cancer (Canadian Cancer Society/National Cancer Institute of Canada, 2005), and 10 to 50% of these deaths

are thought to be directly related to malnutrition rather than the disease itself (Warren, 1932; Klasters et al., 1972; Ignagaki et al., 1974; Ambrus et al., 1975). Malnutrition is a common problem in advanced cancer, so much so that 50 to 90% of cancer patients will experience weight loss during the disease trajectory (Reuben et al., 1988; Curtis et al., 1991; Krech & Walsh, 1991; Donelly & Walsh, 1995; Maltoni et al., 1995; Walsh et al., 2000; Vigano et al., 2000a; Komurcu et al., 2002; Thoresen et al., 2002). Weight loss experienced during the course of cancer is largely the result of cancer cachexia, a wasting syndrome characterized by profound weight loss, specifically of muscle and adipose tissue (MacDonald et al., 2003). The importance of weight loss cannot be overemphasized as it is associated with weakness, reduced functional status, impaired immunity, and reduced survival (De Wys et al., 1980; Reuben et al., 1988; Maltoni et al., 1995; Vigano et al., 2000b; MacDonald et al., 2003). Although wasting in cancer cachexia arises primarily as a result of complex metabolic derangements (Tisdale, 1997; MacDonald et al., 2003; Van Cutsem & Arends, 2005), decreased dietary intake is also a contributing factor (Ravasco, 2004). Reductions in dietary intake likely arise due to the experience of numerous symptoms such as anorexia, early satiety, chemosensory loss and distortion, dry mouth, dyspnea, and dysphagia (Donnelly & Walsh, 1995; Walsh et al., 2000). These symptoms are know to contribute substantially to declines in dietary intake, weight loss, negative energy balance, and malnutrition (De Wys et al., 1980; Maltoni et al., 1995; Reuben, 1988 et al.; Walsh et al., 2002; Vigano et al., 2000b).

1.2 Rationale for Meeting Nutritional Requirements with Therapeutic Foods

With the understanding that reduced dietary intakes contribute, at least in part, to the progressive malnutrition observed in advanced cancer, attempts to improve voluntary dietary intakes of cancer patients have been numerous. The prescription of pharmacological agents such as corticosteroids, progestational agents (Gagnon & Bruera, 1998; Yavuzsen et al., 2005), cannabinoids (Jatoi et al., 2002), the hormone ghrelin (Neary et al., 2004), and supplementation with certain essential amino acids (Cagniano et al., 1996; Yoshida et al., 2001; Eubanks May et al., 2002) have been common strategies. As well, there has recently been a particular focus on the inclusion of long chain *n-3* polyunsaturated fatty acids in nutritional support for cancer patients (Elia et al., 2006). These fatty acids are known to be extremely depleted in these patients (Pratt et al., 2002; Zuijdgeest-van Leeuwen et al. 2002) and some benefits of their supplementation have been described (Wigmore et al., 1996; Gogos et al., 1998; Barber et al., 1999a,b; Wigmore, 2000; Fearon et al., 2003; Jatoi et al., 2004).

The ultimate objective of cachexia therapies, pharmacological and/or nutritional support, is the maintenance or gain of body weight or lean tissue (MacDonald et al., 2003).Unfortunately, these pharmacological and nutritional therapies have had limited success in achieving weight gain in advanced cancer patients (Stratton & Elia, 1999). The following discussion will focus on nutritional therapies, specifically oral nutritional supplements, used in an attempt to improve patient outcomes such as dietary intake and body weight.

1.3 Conventional Nutritional Supplementation Fails to Increase Dietary Intakes

Typical nutrition support strategies for cancer patients include dietary counseling by a registered dietitian to improve energy and protein intakes through dietary modifications. Dietary modifications depend on the patient's tolerance, symptoms experienced, stage of disease, degree of malnutrition, and presence of co-morbid conditions (Martin, 2000). These modifications typically include a high protein-high calorie diet, texture modifications, small frequent meals, and the use of commercial nutritional supplements (Martin, 2000). Oral nutritional supplementation is assumed to be a simple and minimally invasive method to increase dietary intakes (Van der Shueren, 2005) and according to Brown & Radke (1998), was the most frequently recommended nutritional intervention for non-small cell lung cancer patients who received a nutrition assessment from a physician, nurse, or dietitian. Oral nutritional supplements generally take the form of canned liquid products such as Ensure® and Boost®. A typical serving (8 fl. oz. or 237 ml) provides approximately 250 kcal, 9 g of protein (14% energy as protein), and 6 g of fat.

Despite being a common strategy to improve dietary intakes, overall use of these products by advanced cancer patients has been reported to be relatively low – less than 30% (Brown & Radke, 1998; Thoreson et al. 2002; Hutton et al., 2006); indicating this form of nutritional intervention is not habitually employed by this population. Hutton et al. (2006) examined the dietary patterns of 151 advanced cancer patients, and observed on average patients ate meals made up of

foods selected by healthy individuals. Only a specific subset of patients, whose food selection behavior clustered with the consumption of other liquid foods, such as soups and juices, tended to select enteral supplements. The reasons for consumer reaction to these available products are unknown, but may include factors such as lack of awareness of the products availability, palatability, and cost. Additionally, many of the nutritional interventions have not been framed within the context of the current dietary intakes of cancer patients, nor do they take into consideration the many and varied symptoms experienced that comprise impediments to food intake. Understanding food preferences of the target population is critical for the development of nutritional recommendations and products. Therefore, to improve dietary energy and protein intakes it would be essential to consider what advanced cancer patients eat, and to provide nutritional interventions perceived as enjoyable, and possess qualities (e.g. palatability) that facilitate their incorporation into current dietary patterns.

Once in the hands of the consumer, palatability is considered the most important feature of a nutritional supplement (Silk, 1999). It has been identified as a major determinant of meal size and in the initiation of food intake (Padilla, 1986). As well, the palatability and overall acceptance of nutritional supplements are key factors in their effectiveness (Fuller, 1985) i.e. an unpalatable food would provide little motivation for consumption especially in the advanced cancer population who often suffer from a variety of taste and smell alterations (Ravasco, 2005). Another important consideration in the development of a nutritional supplement is the type of satiety feedback information elicited by food, which is

in turn a function of volume, nutrient density, digestion, and metabolism of the component nutrients. In the elderly, liquid oral nutritional supplements or a pre-load condition resulted in compensating reductions in meal intake such that total energy intakes were not improved (Fiatarone Singh et al., 2000; Lauque et al., 2000; Young et al., 2004). Volume and nutrient content of the supplement may have been responsible for the compensatory decline in spontaneous intake from meals (Fiatarone Singh et al., 2000). Changes in gastric physiology and/or alterations in food intake regulation have also been suggested (Wilson & Morely, 2003). To what extent this occurs in cancer patients is unknown - the effect of supplementation on spontaneous meal intakes are rarely reported (Stratton & Elia, 1999; Elia et al., 2006).

Reductions in spontaneous food intake from meals were recently reported by Fearon et al. (2003). The study compared the effect of a control and an experimental enteral nutritional supplement on the loss of weight and lean tissue in patients with advanced pancreatic cancer. Each serving (8 fl. oz. or 237 ml) of the liquid oral nutritional supplement provided 310 kcal, 16 g of protein (20% energy as protein), and 6 g of fat, with (experimental) or without (control) 1.1 g of eicosapentaenoic acid (EPA). Subjects were asked to consume 2 cans (16 fl. oz. or 474 ml) of the supplement per day for 8 weeks; timing of supplement consumption was not specified. Average supplement intake for both the experimental and control groups was ~1.4 cans/d (70% of the prescribed amount). The authors noted significant reductions in spontaneous meal intake with consumption of the control supplement, such that there was no significant

increase in total energy intake; there was however a significant increase in total protein intake. A non-significant decline in spontaneous meal intake and a significant net increase in total energy and protein intakes of 224 kcal/d and 15 g/d were observed in the experimental group. The authors suggested total intakes from meals were linked to the *n-3* fatty acid content of the experimental supplement. The addition of *n-3* fatty acids to the diet has been suggested to produce a mild appetite stimulating effect in cancer patients (Jatoi et al., 2004).

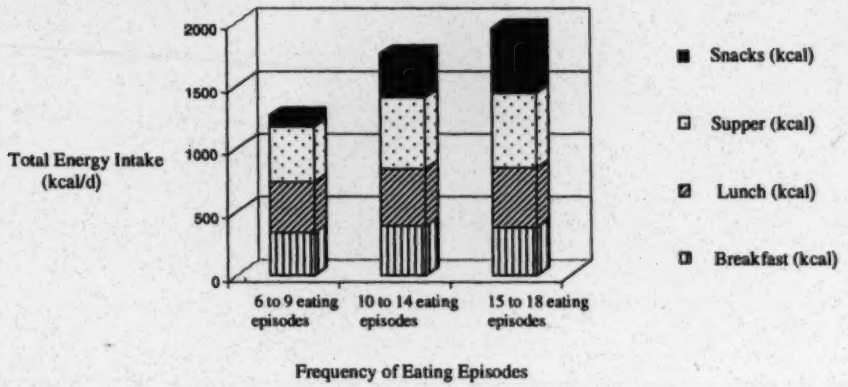
Timing of supplement consumption may also provide an explanation for the reduction of spontaneous food intake from meals. Porini et al. (1997) showed when healthy subjects were fed a preload (omelet) as an appetizer, there was a reduction in total energy consumption from the subsequent meal. On the other hand, when the same preload was fed as a snack two hours before a meal, it failed to produce reductions in energy intake at the subsequent meal. The authors suggested the snack had time to metabolize, and the effect of nutrients on the food-intake control system had dissipated. This may be an important consideration for advanced cancer patients, a snack consumed far from a meal may not contribute to satiety, allowing for an increase in total energy and protein intakes. This effect has also been demonstrated in the elderly; Wilson et al. (2002) suggested supplements consumed between meals instead of with meals may avoid compromising the reservoir function of the stomach, and suggested supplements to be consumed at least one hour before the next meal.

McCarthy & Weihofen (1999) examined the effect of nutritional supplementation on the food intake of cancer patients undergoing radiation

therapy. Subjects were asked to consume an oral liquid nutritional supplement between meals everyday for a total of four weeks. Each serving (8 fl. oz. or 237 ml) of the supplement provided approximately 250 kcal, 8 g of protein (12% energy as protein), and 6 g of fat. Results indicated subjects successfully consumed an additional 500 to 600 kcal/d in supplements, resulting in significant increases in energy and protein intakes compared to controls. Reductions in food derived calorie and protein intakes were reported to be small and non-significant. Consuming the nutritional supplement between meals may have improved subjects' ability to include the supplement without reductions in food-derived calorie and protein intakes. Similar results were reported in a pilot study by Bauer & Capra (2005). Non-small cell lung and pancreatic cancer patients (n = 9) were asked to consume a protein and energy dense, *n-3* fatty acid enriched oral nutritional supplement between meals. The supplement had no effect on meals, resulting in significant improvements in total energy and protein intakes.

Taking advantage of between meal food consumption may be an excellent way to encourage increased energy and protein intakes in cancer patients, who typically experience early satiety. Hutton et al. (2006) observed variations in total energy intakes and eating frequency among advanced cancer patients were largely accounted for by the variation in food consumption between meals. Thus, advanced cancer patients who snacked between meals had significantly higher total caloric intakes compared to those who did not, despite similar meal sizes among groups (Figure 1-1). These observations support the use of between meal snacks as a method to improve total energy and protein intakes.

Figure 1-1. Caloric intake (kcal/d) by meal and frequency of eating episodes over three days. (Adapted from Hutton et al., 2006).



In summary, the development of a nutritional supplement that is highly palatable, typically consumed by advanced cancer patients, and takes into consideration factors that may impact overall satiety (volume, nutrients, and timing of consumption) may contribute to an improved effectiveness in terms of enabling advanced cancer patients to increase dietary energy and protein intakes to meet their recommended nutritional requirements for weight maintenance.

1.4 HYPOTHESIS

This research was undertaken to explore the following hypothesis:

A palatable nutritional supplement, optimized for the clinical features of advanced cancer patients, can successfully be incorporated into their habitual dietary patterns to effectively increase total dietary (energy, protein, and *n-3* fatty acid) intakes.

1.5 OBJECTIVES

The specific objectives of my research were as follows:

1. To develop a protein dense food-based nutritional supplement, and to test the acceptability of this product to cancer patients.
2. To examine the change in total energy and protein intakes before and after supplementation.
3. To examine the change in meal derived energy and protein intakes before and after supplementation.
4. To examine the change in essential *n-3* polyunsaturated fatty acid content, specifically EPA + docosahexaenoic acid (DHA), of plasma phospholipids before and after supplementation.

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CHAPTER TWO

2.0 DEVELOPMENT OF A FOOD-BASED NUTRITIONAL SUPPLEMENT

2.1 RATIONALE FOR THE TYPE OF THERAPEUTIC FOOD

Hutton et al. (2006) represents the only available evidence related to detailed dietary patterns in patients with advanced malignancies. Because conventional enteral supplements were not selected by ~ 70% of subjects, and comprised as little as 2.5% of energy for major subgroups of the population, the food groups selected by cancer patients were studied to identify typical foods that seemed to be preferred. Meat (14.1% of energy) followed by dessert foods (9.8% of energy) were identified as the largest contributors to percent energy intake from a total of 20 food categories (Hutton et al., 2006). We considered dessert-type food items as a potentially attractive vehicle for a food-based nutritional supplement. Other practical considerations of this food type include options for use in snacks, convenience, and ease of consumption.

2.2 RATIONALE FOR THE MACRONUTRIENT LEVELS AND COMPOSITION OF A FOOD-BASED NUTRITIONAL SUPPLEMENT

2.2.1 NUTRITIONAL SUPPLEMENT FOR CANCER PATIENTS

Current dietary macronutrient intakes and the recommended dietary intakes for advanced cancer patients are provided in Table 2-1. In the sections that follow, these are explained.

Table 2-1. Reported dietary macronutrient intakes, and recommended dietary intakes for advanced cancer patients.

	Reported Dietary Intakes	Clinical Guidelines for Dietary Intakes
Energy		
Absolute (kcal/d)	1504 to 1716[c]	
kcal/kg BW/d	25.3[d]	30 to 35[a]
Protein		
Absolute (g/d)	60 to 67.7[c]	
g/kg BW/d	1.0[d]	1.5 to 2.0[a]
EPA + DHA/d		
Absolute (g/d)	0.1 to 0.2[b]	0.5 to 1.8[b]
Energy by Macronutrient		
Carbohydrate (% total energy)	55.0[d]	30 to 70[a]
Fat (% total energy)	29.7[d]	15 to 25[a]
Protein (% total energy)	16.3[d]	20 to 50[a]

[a]Martin (2000)
[b] Kris-Etherton (2002) American Heart Association Recommendations for healthy individuals
[c] Boseus et al. (2001); Fearon et al., (2003); Lundholm et al., (2004); Hutton et al., (2006)
[d]Hutton et al. (2006)

2.2.2 NUTRITIONAL TARGETS FOR PROTEIN

I. PROTEIN REQUIREMENTS ARE INCREASED IN THE TUMOR-BEARING STATE

Protein is a major functional and structural component of all cells in the human body; it is required for tissue maintenance and synthesis, as well as the production of various enzymes, membranes, transport carriers, and hormones. Therefore, an adequate supply of dietary protein is essential to maintain normal body function and health. The current recommended dietary intake for healthy men and women under and over 51 years of age, based on analysis of available nitrogen balance studies, is 0.80 g/ kg BW/d of good quality protein (Institute of Medicine of the National Academies, 2005). Unfortunately, there are several

pathological conditions, such as cancer, for which these requirements do not apply. In clinical dietetic practice, a protein intake between 1.0 and 1.5 g of protein/ kg BW/d is recommended for most cancer patients to help achieve weight maintenance, whereas depleted cancer patients may require upwards of 1.5 to 2.0 g of protein/kg BW/d (Martin, 2000). These recommendations are based on the understanding that protein and amino acid metabolism are altered in the tumor bearing state, thus dietary protein must be increased in order to preserve lean tissue and prevent weight loss.

There are several factors thought to contribute to muscle wasting in cancer cachexia. Current dominant themes include inflammation and certain tumor-derived catabolic factors, which elicit uncontrolled catabolism of protein and lipid containing tissue (MacDonald et al., 2003). These factors are believed to produce alterations in protein and amino acid metabolism that change the pathways of amino acid utilization (Obled, 2002). These alterations result in the rapid wasting of skeletal muscle, which may be attributed to an increased need for specific amino acids i.e. for the synthesis of various proteins, and compounds involved in the inflammatory response (Reeds et al., 1994; Obled, 2002). Although clinical studies on the amino acid metabolism of cancer patients are relatively few, and based on small samples from specific patient populations, it is possible to identify distinctive patterns in amino acid utilization for certain amino acids such as: aromatic, sulfur containing, branched chain, and several non-essential amino acids (alanine, glutamine, cysteine, and arginine) (Mackenzie & Baracos, 2004). Therefore, it is possible that an increase in the dietary intake of these specific

amino acids may reduce the rate of muscle wasting, characteristic of advanced cancer patients (Obled, 2002).

II. Attributes of the Protein Source: Protein Quality, Amino Acid Content, and Effects on Short-Term Satiety

Based on current research it is evident the dietary protein requirements for advanced cancer patients are increased, with an amplified need for specific amino acids. Thus, consumption of a high quality protein source, which best meets the protein and amino acid requirements of the advanced cancer patient, would be an important consideration in the development of a food-based nutritional supplement. In the past, the Protein Efficiency Ratio (PER) was the preferred method for assessing the protein quality of foods in Canada and the United States. The PER determines the effectiveness of a protein through the measurement of animal growth – more specifically the growth of weanling rats (Hoffman & Falvo, 2004). Animals are fed a protein source and weight gain is measured in grams per gram of protein consumed. The value obtained is then compared to a standard value of 2.7 (the standard for casein protein), anything exceeding this value is considered an excellent quality protein (Hoffman & Falvo, 2004). However, this method has been criticized because it fails to provide a strong correlation between growth and the maintenance needs of humans (FAO/WHO, 1991).

Other measures of protein quality have since been described, including the biological value (BV), a measurement of how efficient the body utilizes dietary protein. The biological value is the proportion of nitrogen used for tissue

formation divided by the nitrogen absorbed from food, multiplied by 100 (FAO/WHO, 1991). Therefore, the BV is expressed as the percentage of nitrogen used, and a food with a high BV correlates to a higher supply of the essential amino acids. Net protein utilization (NPU) is another measure of protein quality similar to the BV, except the NPU measures the proportion of nitrogen used for tissue formation from the amount of nitrogen ingested (FAO/WHO, 1991). The weaknesses of these methods lies in the fact they do not take into consideration the factors that influence the digestion of proteins and the interaction of proteins with other foods prior to absorption (Hoffman & Falvo, 2004).

In 1991, the FAO/WHO recognized the limitations of the various measures of protein quality, and adopted the Protein Digestibility Corrected Amino Acid Score (PDCAAS) to assess the protein quality of foods for human consumption. The PDCAAS takes into account the amino acid content and true digestibility of a food, with respect to its ability to supply indispensable amino acids in the amounts necessary to meet human requirements (FAO/WHO, 1991; Tome et al., 2002). A PDCAAS of 1.00 indicates a protein source that meets the reference requirements for all indispensable amino acids, whereas a score below 1.00 indicates the protein source does not meet the requirements for at least 1 of the indispensable amino acids. According to the PDCAAS, high quality protein sources include: casein, egg, milk, soy, and whey (Table 2-2).

Table 2-2. Protein quality rankings according to the protein efficiency ratio (PER), biological value (BV), net protein utilization (NPU), and protein digestibility corrected amino acid score (PDCAAS).

Protein Type	PER	BV	NPU	PCDAAS
Beef	2.9	80	73	0.92
Black Beans	0	-	0	0.75
Casein	2.5	77	76	1.00
Egg	3.9	100	94	1.00
Milk	2.5	91	82	1.00
Peanuts	1.8	-	-	0.52
Soy Protein	2.2	74	61	1.00
Wheat Gluten	0.8	64	67	0.25
Whey Protein	3.2	104	92	1.00

Adapted from Hoffman & Falvo (2004)

The high quality protein sources commonly used in commercially sold liquid oral nutritional supplements, such as Ensure® and Boost®, include casein, whey, and soy. In the development of a food-based nutritional supplement egg protein would also be an important protein source to consider. Egg protein is a high quality protein with an amino acid profile necessary to meet human requirements, and it has been used for many years as the reference protein to which all other proteins are compared (Watkins, 1995).

There may be some advantages to using egg protein, over casein and whey, in a food-based nutritional supplement. First, the amino acid content of egg protein appears to be comparable to that of casein and whey protein for most amino acids (Table 2-3). However, egg protein contains a larger proportion of sulfur amino acids (methionine and cysteine) when compared to casein and whey. This may be important as there is a reduced availability of sulfur-containing

amino acids in the tumor-bearing state, which is attributed to tumor utilization of methionine and cysteine, as well as inadequate dietary protein intakes (Mackenzie & Baracos, 2004). In addition, the aberrant host response to the tumor increases the metabolic demand for sulfur-containing amino acids for the synthesis of glutathione and acute phase proteins (Mackenzie & Baracos, 2004). Egg protein may better reflect the amino acid requirements of the tumor bearing-state.

Table 2-3. Amino acid content of egg albumen powder, whey protein powder, and casein protein powder (mg amino acid/100 g powder).

Amino Acids	Egg Albumen Powder[a] (mg/100 g)	Whey Powder[b] (mg/100g)	Casein Powder[b] (mg/100g)
Alanine	4.96	4.8	3.1
Arginine	4.65	2.3	3.8
Aspartate	8.22	10.2	7.3
Cysteine	2.17	1.2	0.4
Glutamate	10.54	17.2	22.3
Glycine	2.79	2.0	1.9
Histidine	1.86	1.6	3.2
Isoleucine	4.34	8.4	5.8
Leucine	6.82	10.5	10.1
Lysine	5.12	9.1	8.3
Methionine	3.02	1.6	3.0
Phenylalanine	4.73	3.1	5.4
Proline	3.10	6.1	10.5
Serine	5.50	5.2	6.3
Threonine	3.64	6.2	4.6
Tryptophan	1.32	2.1	1.4
Tyrosine	3.18	2.4	5.8
Valine	5.58	6.0	7.4
Aromatic AA (Phe, Tyr, Trp)	9.23	7.6	12.6
Sulfur AA (Met, Cys)	5.19	2.8	3.4
Branched Chain AA (Leu, Ile, Val)	16.74	24.9	23.3

[a]Watkins (1995), [b]Hall et al. (2003)

Second, egg protein can be easily incorporated into a number of recipes, such as custards, quiches, and soufflés to make food-based nutritional supplements that are palatable i.e. lack the institutional flavor often associated with other forms of oral liquid or powder supplements, and allows the use of recipes based around foods that are habitually consumed by the advanced cancer population e.g. dessert foods. Third, casein has a BV of 77 and a net protein utilization of 76, whereas egg and whey protein have BVs of 100 and 104 and net protein utilization of 94 and 92 respectively (Table 2-2). This may indicate that egg (and whey) protein are better retained and utilized for tissue formation when consumed as part of the diet compared to casein. Manary et al. (2004) demonstrated when malnourished children with acute infection were fed a diet containing egg or casein protein; egg protein resulted in a slower rate of leucine oxidation i.e. less waste of amino acids when compared to children fed a diet containing casein protein. Egg protein may provide a greater proportion of amino acids thought to be limiting in inflammatory states, thereby better meeting the requirements for tissue formation when compared to casein protein.

Although egg and whey protein appear to be similar in terms of their PDCAAS, BVs, and net protein utilization, egg protein may have a reduced impact on satiety when compared to whey; an important consideration as greater than 50 percent of advanced cancer patients experience early satiety (Walsh et al., 2000), which in turn contributes to reduced energy and protein intakes. It is well established, in humans, that protein is the most satiating macronutrient (Booth et al., 1970; Hill & Blundell, 1986; De Castro, 1987; Rolls et al., 1988; Barkeling et

al., 1990; Johnstone et al., 1996; Stubbs et al., 1996; Vandewater & Vickers, 1996; Porini et al., 1997; Latner & Schwartz, 1999). Although, little investigation in to the effect of protein source on the short-term feeding response has been carried out in humans, there is some support from both animal and human studies. In rats, the greatest degree of food intake suppression within the next hour of feeding, occurred following a gavage with whey protein, followed by egg-albumin, soy, and casein protein (Anderson & Moore, 2004). Likewise in humans, Anderson et al. (2004) demonstrated compared with a water control, preloads of 45 to 50 g of whey and soy protein, but not egg albumen, suppressed food intake at a pizza meal consumed 1 hour later. As well, the egg albumen preload, in contrast to whey and soy preloads, increased cumulative energy intake relative to the water control.

A likely explanation for the lack of effect of egg albumen on the suppression of food intake may be the reduced effect of egg albumen on satiety hormones such as cholecystokinin (CCK) and insulin. In humans, egg whites, in contrast to whole egg or egg yolk, did not raise the blood concentrations of CCK (Pelletier et al., 1996). As well, the consumption of eggs at breakfast resulted in lower plasma insulin concentrations compared to the consumption of ham (Villaume et al., 1986). Hall et al. (2003) also demonstrated an effect of protein source on satiety; equivalent preloads (48 g) of whey or casein protein, resulted in a significant reduction in energy intake at a buffet style lunch 90 minutes later. Subjects also reported greater subjective satiety after the consumption of the whey preload compared to the casein preload. As well, plasma CCK increased by 60 percent,

and glucagon-like peptide (GLP) and glucose-dependent insulinotropic polypeptide (GIP) increased by 36 percent following consumption of the whey compared to the casein preload. This is an important observation as CCK and GLP are gastrointestinal satiety signals responsible for reducing food intake. Therefore, egg protein (egg albumen) may have less of an impact on satiety when compared to whey protein.

In summary, egg protein is a practical protein source for use in the development of a food-based nutritional supplement for several of reasons: 1) it is a high quality protein with an appropriate amino acid content to reflect the increased requirements in the tumor bearing state, 2) egg protein can be easily incorporated into food-based recipes, such as custard, 3) it may be better retained when compared to casein, 4) egg protein may be less satiating when compared to whey protein.

III. Protein Requirements

According to Millward (2004), dietary protein intake is determined by overall food energy intake, which varies throughout the lifecycle. Unfortunately, aging is associated with reduced energy intakes, and nitrogen retention is dependent on energy intake (Calloway, 1975). It has been suggested, for the elderly, that the protein density of the diet should increase as total energy intakes decrease to prevent the risk of developing protein deficiencies, and to compensate for lower nitrogen retention capacity associated with reduced energy intakes (Millward, 2004; Morai et al., 2006). However, the diets of older, healthy individuals with

lower energy intakes, generally fail to meet their protein requirements at a level of consumption required to meet their energy needs (Millward, 2004). In clinical dietetic practice, a protein intake between 1.5 g/kg BW/d and 2.0 g/kg BW/d is recommended for estimating the protein needs of depleted cancer patients (Martin, 2000). The mean protein intake for advanced cancer patients is approximately 1g/kg BW/d (Bosaeus et al., 2002; Fearon et al., 2003; Hutton, et al. 2006), indicating the majority of advanced cancer patients fail to meet the minimum requirements for weight maintenance. According to Millward (2004) and Morais et al. (2006), protein intakes at this level are insufficient to support nitrogen balance even in healthy individuals of the typical age of cancer patients (65 to 70 years of age). Therefore, a nutritional supplement would need to provide at least an additional 0.5 g/kg BW/d or ~35 g of protein/d to meet the minimum protein requirement. This amount of protein is similar to the protein content (25 to 32g/d) of liquid oral nutritional supplements used in clinical research studies (Ovesen & Allingstrup, 1992; Barber et al., 1999a; Fearon et al., 2003).

2.2.3 Nutritional Targets for Carbohydrate

I. The Effect of Carbohydrate on Nitrogen Balance

When developing a nutritional supplement for advanced cancer patients it is also important to consider the effect other macronutrients will have on the utilization and retention of protein for the promotion of a positive nitrogen balance. Increasing the protein content of the diet should be accompanied by a

concurrent increase in energy, to support nitrogen retention and energy requiring physiologic processes such as protein synthesis (Calloway, 1975; Prod'homme et al., 2004; Millward, 2004). Carbohydrates appear to have a nitrogen sparing effect, being more effective when compared to fat, at least for healthy individuals. No such data are available for cancer patients, but since most cancer patients are in a negative energy balance, the most comparable studies in healthy humans may be those in which the subjects were fed at sub-maintenance dietary energy and protein levels. Richardson et al. (1979) fed healthy young men at sub-maintenance dietary energy and protein levels, supplying two times as much energy from carbohydrate as from fat (2:1). There was a significant improvement in nitrogen utilization and overall nitrogen balance, compared to an isonitrogenous diet that provided equivalent amounts of energy from carbohydrate and fat (1:1). On the other hand, a study similar in design to that of Richardson et al. concluded that the nitrogen balances' of healthy subjects fed 75 percent of their maintenance energy requirements, were similar when fed a diet containing either a carbohydrate to fat ratio of 2:1 or 1:1 (McCargar et al., 1989). Carbohydrates, on the one hand, have been suggested to promote protein synthesis secondary to induced insulin secretion, while fatty acids are suggested to inhibit amino acid oxidation. Which of these would prevail in a cancer patient is unknown. In the development of the food-based nutritional supplement we attempted to maintain a carbohydrate to fat ratio as close to 1:1 as permitted by the recipe formulation.

II. ENERGY REQUIREMENTS

By the time an individual is classified as having advanced cancer, they are likely to be malnourished and to have experienced significant depletion, from pre-illness state, of muscle and fat stores. According to the clinical dietetic practice guidelines, the recommended energy requirement for weight maintenance in malnourished cancer patients lies between 30 to 35 kcal/kg BW/d (Martin, 2000). Lundholm et al. (2004) recently reported that approximately 34 kcal/kg BW/d was necessary to support weight maintenance in a large sample of patients with untreatable malignant disease. Similarly, Fearon et al. (2003) were able to stabilize the weights of patients with unresectable pancreatic cancer, who were otherwise losing weight at a rate of 3.3 kg BW/month, by raising total energy intakes to 35 kcal/kg BW/d. The mean energy intake of advanced cancer patients ranges from 24 to 26 kcal/kg BW/d (Bosaeus et al., 2002; Fearon et al., 2003; Lundholm et al., 2004; Hutton et al., 2006), indicating the majority of advanced cancer patients fail to meet the minimum energy requirements necessary to support weight maintenance. A nutritional supplement would need to provide an additional ~10 kcal/kg BW/d or ~ 600 kcal/d, in order to meet the recommended requirements for weight maintenance. The suggested amount of energy is similar to the energy content (500 to 620 kcal/d) of the liquid oral nutritional supplements used in clinical research studies (Ovesen & Allingstrup, 1992; Barber et al. 1999_a; Fearon et al, 2003).

2.2.4 Nutritional Targets For Eicosapentaenoic Acid (EPA) and Docosahexaenoic Acid (DHA)

I. N -3 Fatty Acids as a New Approach for Cancer-Associated Wasting

With an understanding that inflammation plays a major role in cancer-associated wasting, research has focused on the properties of *n*-3 fatty acids. Fatty acids of the *n*-3 type have anti-inflammatory properties, which may attenuate some of the mediators of systemic inflammation such as proinflammatory cytokines (tumor necrosis factor-α, interleukin-1, interleukin-6, and interferon-γ), proinflammatory eicosanoids, and the tumor-derived proteolysis-inducing factor (Barber, 2001; McDonald et al., 2003). These mediators of inflammation are believed to be responsible, in part, for promoting energy imbalance and muscle wasting in advanced malignant disease. A new approach in the management of cancer associated wasting includes the administration of fish oil and essential long chain *n*-3 fatty acids EPA and DHA, which appear to attenuate some of the mediators of inflammation. Although the fatty acid status of advanced cancer patients has not been well characterized, available data have shown advanced cancer patients to be extremely depleted in *n*-3 fatty acids (Pratt et al., 2002; Zuijdgeest-van Leeuwen et al. 2002). These observations are consistent with the rationale for supplementing with *n*-3 fatty acids, which may lead to the production of less inflammatory compounds and improvements in fatty acid status (Barber, 2001).

In a series of clinical trials in cancer patients, supplementation with fish-oil capsules, high purity EPA, or oral liquid nutritional supplements enriched with

fish-oil resulted in weight stability or modest weight gain (Barber et al., 1999a; Wigmore et al., 1996; Wigmore et al., 2000); attenuation of the acute phase protein response and stabilization of resting energy expenditure (Barber et al., 1999b; Wigmore et al., 1996); and an improvement in appetite (Barber et al, 1999a; Jatoi et al., 2004). Additionally, supplementation with fish oil significantly prolonged survival for severely ill patients with generalized malignancy (Gogos et al., 1998). Therefore, the incorporation of *n*-3 fatty acids into a nutritional supplement may be a beneficial ingredient for attenuating some of the mediators of inflammation associated with energy imbalance and muscle wasting, and may also induce improvements in appetite.

II. Recommendations for EPA and DHA

The American Heart Association's recommendations to reduce subsequent cardiac and all cause mortality for healthy individuals includes the intake of 0.5 to 1.8 g of EPA and DHA/d (Kris-Etherton et al., 2002). Currently, there is no consensus regarding the amount of EPA and DHA necessary to achieve beneficial effects in terms of weight gain, appetite, and the attenuation of mediators of inflammation in advanced cancer patients. However, the amount of EPA and DHA used in previous supplementation studies for pancreatic and advanced cancer patients ranged from 2 to 4.7 g of EPA/d, and 0.92 to 2.8 g of DHA/d in the form of fish-oil capsules, high purity EPA, or oral liquid nutritional supplements (Wigmore et al., 1996; Gogos et al., 1998; Barber et al., 1999a;

Wigmore et al., 2000; Bruera et al., 2003; Fearon et al., 2003; Burns et al., 2004; Jatoi et al., 2004).

Incorporation of EPA and DHA in to a food-based nutritional supplement may improve intakes of EPA and DHA, which are not readily accessible in diets that are not predominantly fish-based. As well, incorporating EPA and DHA into supplement format may help to limit the side effects associated with the ingestion of large fish-oil capsules. The most common side effects associated with fish-oil capsules include fishy aftertaste, gastrointestinal upset, and nausea, all of which tend to increase with increasing dosage (Kris-Etherton et al., 2002).

Previous studies using oral liquid nutritional supplements have provided approximately 3 g of EPA and DHA/d (Barber et al., 1999b; Fearon et al., 2003; Jatoi et al., 2004; Bauer & Capra, 2005). For the present study, a smaller dose of EPA and DHA was selected for incorporation into a food-based nutritional supplement, as there are limitations to the amount of EPA and DHA that could be provided with the selected ingredients while continuing to maintain palatability. The goal was to have a supplement with an EPA and DHA content similar to the amount of EPA (1.5 g/d) associated with the prevention of body weight and lean tissue loss in pancreatic cancer patients (Fearon et al., 2003). It is important to note the levels of EPA and DHA used in the food-based nutritional supplement are not meant to provide the therapeutic doses necessary to achieve significant improvements in clinical outcomes such as weight gain and survival. The main goal of the food-based nutritional supplement is to provide a palatable supplement that will improve total *n*-3 fatty acids dietary intakes.

2.3 FOOD-BASED NUTRITIONAL SUPPLEMENT DEVELOPMENT

The food-based nutritional supplement selected for this research project could have taken many forms, however our initial approach was baked vanilla custard. The original conception of the recipe formulation was to have a macronutrient composition comparable to the liquid oral nutritional supplements used in other clinical research studies (Table 2-4).

Table 2-4. Nutrient composition of a liquid oral enteral supplement enriched with *n-3* fatty acids (Barber et al., 1999a; Fearon et al., 2003; Bauer & Capra, 2005).

	Oral Enteral Supplement
Volume (ml)	237
Total Calories (kcal)	310
kcal per ml	1.3
Total Protein (g)	16
% energy as protein	20
Total Fat (g)	6
Total EPA content (g)	1.1

The vanilla custard differs from traditional oral liquid supplements in several aspects: 1) it is a highly palatable food, in-line with the food preferences of advanced cancer patients 2) a good vehicle for providing energy and high quality protein in the amounts necessary for advanced cancer patients to meet their nutritional requirements for weight maintenance 3) uses egg albumen as the main protein source, a protein with a low satiety index but rich in essential amino acids, especially sulfur-containing amino acids 4) permits the use of ingredients

that enable the incorporation of the essential *n*-3 fatty acids EPA and DHA 5) has a smaller total volume, which may reduce the effect of early satiety.

2.3.1 Consumer Sensory Evaluation of the Vanilla Custard Supplement

Development of the vanilla custard took place in the research kitchen of the Human Nutrition Unit at the University of Alberta (Edmonton, Alberta, Canada). Prior to commencing the nutrition intervention study, a consumer sensory evaluation was completed at the Cross Cancer Institute (Edmonton, Alberta, Canada) to determine overall acceptability of the supplement to cancer patients. The primary goal of consumer sensory research is to enhance the quality of a product by improving specific characteristics as they are perceived by the consumer. A consumer sensory evaluation was conducted to provide guidance for product improvement, and to identify the degree of acceptance for specific characteristics such as sweetness, flavor, consistency, and portion size. It was also important to establish the feasibility of carrying out a nutrition intervention that would require consumption of two daily portions of the vanilla custard. The characteristics sweetness, vanilla flavor, consistency, and portion size were evaluated using the "just about right" scales for attributes (1 = too little of a characteristic, 4 = just about right, 7 = too much of a characteristic), which allowed assessment of the intensity of an attribute relative to some mental criterion of participants; a rating of "just about right" (or 4 out of 7) is ideal.

Overall acceptability of the nutritional supplement was assessed using the category hedonic scale for acceptance test (1 = dislike extremely, 4 = neither like/dislike, 7 = like extremely), which determined how well the product was liked by participants; a rating of 5 or greater is ideal for the overall liking of the supplement. Additionally, basic sensory information was collected to determine if taste and smell alterations played a role in the overall acceptability of the vanilla custard. Specific questions were selected from a survey tool used to evaluate chemosensory dysfunction in AIDS patients developed by Heald et al. (1998).

A total of 60 individuals, diagnosed with cancer, took part in the consumer sensory evaluation of the vanilla custard. Subjects were recruited using posters advertising the taste testing sessions, placed in high traffic areas around the Cross Cancer Institute. During sensory evaluation sessions participants were provided with 1) an information sheet (Appendix A) listing the purpose of the sensory evaluation and the list of ingredients, 2) a sensory evaluation questionnaire (Appendix B), 3) a portion of vanilla custard to sample.

Of the 60 participants, 25% (n=15) reported changes in their sense of smell and 51.7% (n=31) reported changes in their sense of taste. Alterations in the sense of taste were characterized based on how individuals' rated changes in the four basic tastes (sweet, salty, sour, and bitter) since their cancer diagnosis (Table 2-5).

Table 2-5. Reported changes in the four basic tastes (sweet, salt, sour, bitter) in a sample of individuals diagnosed with cancer, who participated in a consumer sensory evaluation.

Basic Tastes	Number of respondents	Percent (%)
Sweet		
Stronger	11	19.6
As strong	40	71.4
Weaker	5	9.0
I cannot taste at all	0	0
Salt		
Stronger	11	19.3
As strong	35	61.4
Weaker	10	17.5
I cannot taste at all	1	1.8
Sour		
Stronger	10	16.9
As strong	44	74.6
Weaker	5	8.5
I cannot taste at all	0	0
Bitter		
Stronger	15	25.9
As strong	37	63.8
Weaker	5	8.6
I cannot taste at all	1	1.7

On average, alterations in the four basic tastes are relatively common in cancer patients with ~ 36 to 39% of respondents reporting changes in their ability to taste salt and bitter respectively, and ~ 26 to 29% of respondents reporting changes in their ability to taste sour and sweet respectively. Individuals who reported changes in their sense of taste were more likely to report sweet, sour, and bitter tasting stronger now compared to before their cancer diagnosis, whereas the changes for salt were reported equally as being either stronger or weaker compared to before their cancer diagnosis.

Results from the sensory evaluation of the vanilla custard are provided in Table 2-6.

Table 2-6. Results from the consumer sensory evaluation for the vanilla custard. Results are presented as the mean score and standard deviation for each characteristic (sweetness, vanilla flavor, consistency, portion size), and for the overall acceptance of the vanilla custard.

Sensory Evaluation Questions	Number of Respondents	Mean	SD
How sweet is the custard?	60	4.5	1.1
How strong is the vanilla flavor?	60	3.6	1.2
The consistency of custard is:	59	4.2	0.7
The portion size as a snack is:	58	4.9	1.3
How much do you like custard?	60	5.6	1.2

Overall, the supplement was liked (≥5 out of 7 on the hedonic scale) by 83% (n=50) of respondents; however 33% (n=20) of respondents found the supplement too sweet (>4 out of 7 on the just about right scale), 31% (n=19) found the vanilla flavor too mild (<4 out of 7 on the just about right scale), and 36% (n=28) found the portion size too large (>4 out of 7 on the just about right scale). Additionally, 64% (n=38) of participants indicated they could eat two daily portions of the vanilla custard. Of the 36% (n=21) who indicated they could not consume two daily portions of the vanilla custard, several indicated they could consume half a portion twice daily.

From the results of the consumer sensory evaluation, the nutritional supplement was revised to reduce the level of sweetness, increase the intensity of vanilla flavor, and to reduce portion size. Reducing the portion size was an important consideration as evidence suggests short-term intake is affected more

by weight or volume of the food than the energy density (Rolls et al., 1998; Rolls et al., 2000; Rolls et al., 2002; Bell et al., 2003; de Castro, 2005).

2.3.2 Nutrient Composition of Vanilla Custard

The list of ingredients and nutrient composition for 1 serving of the vanilla custard and the daily supplement prescription are presented in Table 2-7.

Table 2-7. Ingredients, macronutrient content, and energy density of the vanilla custard. Presented as the amount per serving and the amount of vanilla custard prescribed per day.

	Amount per serving (140 g/serving)	Amount prescribed per day (280 g/d)
Ingredients		
Cream (18% B.F.)	50 ml	100 ml
Omega-3 enriched liquid egg product (Naturegg™ Break-Free Omega-3™, Burnbrae Farms Ltd., Canada)	50 ml	100 ml
White granulated sugar	25 g	50 g
Egg albumen powder (Innovatech Egg Products Ltd., Canada)	10 g	20 g
Microencapsulated fish oil (Omega-3 powder, Ocean Nutrition Canada Ltd.)	10 g	20 g
Artificial Vanilla Flavor (Creamy Vanilla, Givaudan Canada Co.)	0.325 ml	0.650 ml
Macronutrient Content		
Total Energy (kcal)	329	658
Carbohydrate (g)	26	52
% of total energy	32	32
Protein (g)	17	34
% of total energy	21	21
Fat (g)	17	34
% of total energy	47	47
SFA	8.2	16.4
MUFA	4.2	8.4
PUFA	2.6	5.2
n-6	0.3	0.6
n-3	2.3	4.6
EPA	0.47	0.94
DHA	0.38	0.76

SFA, saturated fatty acids; MUFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids; *n*-6, *n*-6 fatty acids; *n*-3, *n*-3 polyunsaturated fatty acids.

Ingredients were selected to develop a standardized recipe for the vanilla custard that would have a macronutrient content similar to the liquid oral nutritional supplement enriched with *n*-3 fatty acids used in other clinical research studies (Barber et al., 1999a; Fearon et al., 2003; Bauer & Capra, 2005b). In the development of the vanilla custard, cream (18% B.F.) was used to maintain a similar energy content with a smaller portion size. As well, several ingredients were incorporated into the recipe to ensure the supplement would be enriched with the essential fatty acids EPA and DHA. Two ingredients contributed to the EPA and DHA content of the supplement: a liquid egg product enriched with fish oil (Naturegg™, Break-Free Omega-3™, Burnbrae Farms Ltd., Canada) and a microencapsulated fish oil powder (Omega-3 Powder, Ocean Nutrition Canada Ltd., Canada) provided a total of 0.26 g and 0.60 g of EPA and DHA/serving respectively. Several ingredients contributed to the protein content of the vanilla custard: egg albumen powder (Sprayed dried egg albumen, Inovatech Egg Products Ltd., Canada) (7.6 g), liquid egg product enriched with fish oil (4.8 g), omega-3 powder (3.4 g), and cream (1.3 g). The vanilla custard was baked, in a preheated oven (250°F), in batches of 4 or 6 for a total of 63 minutes. Each portion of vanilla custard was baked in 6 oz. plastic polypropylene containers (ELLIPSO™ portion cups, Bunzl Canada Inc.), and placed in a water bath (filled to custard line) to ensure slow, even heating.

The optimized nutritional supplement was then employed in a nutritional intervention study, designed to examine the effect of the nutritional supplement on the total dietary intakes and habitual meal intakes of advanced cancer patients.

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CHAPTER 3

3.0 DO DIETARY SUPPLEMENTS ADD TO OR REPLACE INTAKE AT REGULAR MEALS? A STUDY IN PATIENTS WITH ADVANCED CANCER.

3.1 INTRODUCTION

The course of advanced cancer is associated with progressive malnutrition, with a large proportion of patients developing cachexia, a wasting syndrome characterized by profound loss of muscle and adipose tissue (MacDonald et al., 2003). While it is clear that abnormalities in macronutrient metabolism promote wasting (MacDonald et al., 2003), reduced food intake is also a major contributing factor. Reported mean dietary intakes of cancer patients (Bosaeus et al., 2002; Fearon et al., 2003; Lundholm et al., 2004) are similar to the basal metabolic rates of the same or similar cancer patient populations (Hyltander et al.; 1991, Barber et al., 1999a; Bosaeus et al., 2002; Hutton et al., 2006; Lundholm et al., 2004). Thus, half of patients will typically have insufficient energy intakes to support basal metabolism. In addition, typical protein intakes are ~ 1.0 g protein/kg BW/d, which falls short of recommendations (1.5 to 2.0 g protein/kg BW/d) (Martin, 2000). These levels would be expected to be insufficient to support nitrogen balance even in healthy individuals of the typical age of cancer patients (65 - 70 years, Millward, 2004).

Current therapeutic interventions have focused on improving dietary intakes by enhancing spontaneous food intake using orexigens (Yavuzsen, 2005) or through nutritional supplementation (Elia et al., 2006). Oral nutritional supplementation is assumed to be straightforward (Van der Shueren, 2005),

however patients tend not to select these products (Brown & Radke, 1998; Thoreson et al., 2002), discontinue their use, or show poor compliance (Arnold & Richter, 1989; Fearon et al., 2003; Ravasco et al., 2005). While the underlying reasons for these behaviours are poorly characterized, cancer patients suffer from a variety of nutrition impact symptoms (e.g. chemosensory dysfunction, early satiety, anorexia, nausea), which may affect intake and perceived palatability of nutritional supplements (Walsh et al. 2000; Ravasco, 2005). Introducing a supplement may result in reductions in habitual meal intake, thereby producing no net increase in dietary intakes (Elia et al., 2006; Fearon et al., 2003; Stratton & Elia, 1999).

A number of issues relate to the composition of dietary interventions. Given the loss of lean tissue mass is a central theme in cachexia literature, and the main objective of most cachexia therapies is the maintenance or gain of body weight or lean tissue (MacDonald et al., 2003), there appears to be a lack of attention given to protein in the literature on nutritional supplementation. Importantly, the fraction of protein in some popular enteral supplements (~14 to 16% of energy) may not be higher than the typical diet chosen by these patients (Fearon et al. 2003); therefore these supplements would not differentially increase dietary protein intakes. There has recently been a particular focus on the inclusion of long chain *n-3* polyunsaturated fatty acids in nutritional support for cancer patients, as these fatty acids are known to be depleted (Pratt et al., 2002; Zuijdgeest-van Leeuwen et al. 2002) and some benefits of their supplementation

have been proposed (Wigmore et al., 1996; Gogos et al., 1998; Barber et al., 1999a,b; Fearon et al., 2003; Jatoi et al., 2004).

Here, we hypothesized that the macronutrient intake of a group of advanced cancer patients would be raised using a nutritional supplement specifically enriched in protein and long chain *n-3* polyunsaturated fatty acids. The initial design of the nutritional product was based on the premise that it would take the form of a food (custard) known to be desirable (Payet et al., 2004), and took into account known features of the patient population. Through a series of consumer sensory panels the nutritional product was optimized to the taste preferences of this population. Particular attention was paid to the evaluation of compensating reductions in meal intake during the supplementation period.

3.2 METHODS

3.2.1 NUTRITIONAL SUPPLEMENT DEVELOPMENT

We have observed that cancer patients, similar to those described here, select dessert foods as the second largest contributor to overall energy intakes (out of 20 food categories), indicating a preference for sweet foods (Hutton et al., 2006). We thus developed a dessert-type nutritional supplement (vanilla custard, Chapter 2, Table 2-7) in the research kitchen of the Human Nutrition Research Unit at the University of Alberta (Edmonton, Alberta, Canada). The product was designed to have an energy, protein, and *n-3* fatty acid content similar to that of

enteral nutritional supplements used in other studies (Barber et al., 1999a; Fearon et al., 2003; Bauer & Capra, 2005).

3.2.2 PATIENTS

The study was approved by the Alberta Cancer Board Research Ethics Board. All patients were English speaking, and provided written informed consent. Twelve patients with advanced cancer (defined as metastatic or locally recurrent) were recruited from the Cross Cancer Institute, a cancer treatment centre serving Edmonton and Northern Alberta, and from the Regional Palliative Home Care Program serving Edmonton. Patients were included if they experienced a weight loss of $\geq 5\%$ in the previous six months, were > 18 years of age, and capable of oral intake. Exclusion criteria included obstruction at any point along the gastrointestinal tract, Type 1 or Type 2 diabetes mellitus, and allergies/intolerances to dairy or egg products. Patients with the potential for abnormal absorption were also excluded (ileostomy or intestinal resection above the ileoceacal valve).

3.2.3 RESEARCH DESIGN

A within subject design was used; each subject acted as their own control. Patients completed a baseline assessment period (4 d) followed by a supplementation period (8 d). Baseline assessments included the collection of information (age, sex, height, weight, and diagnosis) from medical charts, and the completion of 3 questionnaires: the scored Patient-Generated Subjective Global

Assessment (PG-SGA, Ottery, 1996, Appendix C); self-perceived taste and smell dysfunction questionnaire (Heald et al., 1998, Appendix D); and the Edmonton Symptom Assessment Scale (ESAS, Bruera et al., 1991, Appendix E).

Dietary intakes, a 24-hour urine collection, and a blood sample were taken on two occasions; baseline and during the last 3 days of supplementation. Urinary urea nitrogen (UUN) excretion was measured with urea reagent and spectrophotometer (SYNCRON LX Systems, Fullerton, CA), and used to evaluate the accuracy of diet records and compliance to the nutritional prescription; UUN excretion is largely determined by the dietary intake of protein nitrogen (Middendorf et al., 1986). Comparison between UUN and diet records provided information regarding recording accuracy, and a change in 24-hour UUN excretion from baseline provided an indicator of supplement consumption. Blood samples were collected to determine changes in fatty acid composition of plasma phospholipids (PL), which are sensitive to changes in dietary fatty acid intake (Clandinin et al., 1983; Pratt et al., 2002; Arab, 2003).

The analysis of plasma PL fatty acids was performed by liquid gas chromatography and described in detail elsewhere (Pratt et al., 2001). In brief, plasma fatty acids were extracted using chloroform/methanol and serum PL isolated on G-plates. A C17:0 standard was added to the scraped serum PL, followed by direct methylation. Fatty acid methyl esters were separated by automated liquid gas chromatography, and the peaks of fatty acid methyl esters were identified by comparison with the standard.

During supplementation patients were asked to consume 2 portions of supplement per day (see Chapter 2, Table 2-7). Seven days is an appropriate length of time to adequately assess changes in macronutrient intakes (McCarthy & Weinhofen, 1999). Patients were instructed to consume the supplement at least 90 minutes before planned meals, with the intent of avoiding compromising the reservoir function of the stomach, thereby reducing the impact on satiety (Wilson et al., 2002). Patients recorded the amount of each portion consumed as 0%, 25%, 50%, 75%, or 100%, and acceptance of each supplement portion was rated using the category hedonic scale (Appendix F).

3.2.4 DIETARY INTAKE

Dietary intakes at baseline and during supplementation were measured using prospectively collected three day diet records, which have been shown to adequately reflect current dietary intake (Bruera et al., 1986; Buzzard, 1998). A registered dietitian instructed patients how to maintain records by estimating food quantities with reference to standard household measures and portion sizes. Diet records were reviewed by the registered dietitian and with patients to ensure completeness. Nutrient content of all food items were estimated using Food Processor SLQ© nutrition analysis software with the Canadian Nutrient File (Esha Research, Salem, Oregon). Mean macronutrient intakes from spontaneous food intake were calculated at baseline and during supplementation. Total dietary intake during supplementation was calculated by adding the reported amount of supplement consumed to the recorded habitual food intake.

3.2.5 Statistical Analysis

Previous work from our research group determined the dietary intakes of advanced cancer patients to be normally distributed (Hutton et al., 2006). Statistical analysis was conducted using SPSS for Windows (version 13.0, SPSS Inc., Chicago). All subjects served as their own control, and Student's paired t-tests were used to compare differences between dietary intakes, 24-hour UUN excretion, and the phospholipid fatty acid profiles between baseline and the supplementation period. Student's t-tests were used to compare the means of unpaired data. Statistical significance was reported at $p<0.05$ (two-tailed).

3.3 Results

3.3.1 Patients

Nineteen subjects enrolled in the 12-day intervention study. Reasons for refusal to participate included: no desire to participate in research studies, poor clinical condition, and poor oral intake. Four patients withdrew due to decline in clinical condition, and three subjects failed to complete the study. A total of 12 patients were included in the analysis (Table 3-1). At the time of writing, 33% (n=4) of patients were surviving, the average interval between participation in this study and death was 142 days, which is similar to patients in our related research. According to the scored PG-SGA, 2 patients were classified as well nourished but at risk for malnutrition, 3 patients were moderately malnourished, and 7 patients were severely malnourished. Half of the patients (6/12 patients) rated their

activity and function as "not my normal self, but able to be up and about with fairly normal activities" (average activity and function score 1.7/4). The most frequently reported nutrition impact symptoms included: early satiety (6/12 patients), constipation (5/12 patients), and anorexia (4/12 patients). Other symptoms including nausea, pain, and diarrhea were reported less frequently (≤3/12 patients). On the taste and smell dysfunction questionnaire, all patients reported at least some type of abnormality in their sense of taste, and half of the patients (6/12 patients) also reported some type of abnormality in their sense of smell. Baseline ESAS scores (mean, SD) were scored on a categorical scale from 0 to 10 (0=absence of symptom; 10=worst possible symptom): pain (1.6 SD 2.4), tiredness (2.8 SD 3.2), nausea (0.3 SD 0.9), depression (1.3 SD 2.0), anxiety (0.7 SD 1.0), drowsiness (1.8 SD 2.2), appetite (3.2 SD 2.3), wellbeing (2.8 SD 2.8), and shortness of breath (2.0 SD 3.0). Average baseline dietary intakes for this study are slightly higher than dietary intakes reported in larger studies (Bosaeus et al., 2002; Fearon et al., 2003; Hutton et al., 2006; Lundholm et al., 2004). However, average contribution of protein to total energy intake was relatively low in comparison (~14% compared to ~16%).

Table 3-1. Baseline characteristics of advanced cancer patients who participated in the nutrition intervention study (n = 12).
(Mean values and standard deviations)

Subject Characteristics	Mean	SD
Age (years)	65	10
Height (cm)	169	6
Weight (kg)	62	11
Weight loss in previous 6 months (%)	9	3
BMI (kg/m^2)	22	3
PG-SGA score	10	6
Meal Intake		
kcal/d	1949	554
kcal/kg BW/d	33	13
g protein/d	69	27
g protein/kg BW/d	1.2	0.6
	(n)	
Male	8	
Female	4	
Tumour Site		
Lung	6	
Colorectal	3	
Breast	1	
Esophageal	1	
Stomach	1	

BMI, body mass index; PG-SGA, patient generated-subjective global assessment; BW, body weight.

3.3.2 Supplement Intake

Reported supplement consumption was 98% (SD 1.5) of the prescribed daily intake. Supplement intake is presented in Table 3-2. Compliance overall (n=12) was supported by an increase in protein intakes estimated from diet records (30 SD 22 g protein from baseline; P=0.001) and 24h-hour UUN excretion (35 SD 43 g protein from baseline; P=0.017). Average preference for the vanilla

custard over the 7 day supplementation period was 6 (SD 0.8) out of 7 on the category hedonic scale for acceptance. In fact, the average individual ratings never fell below 4 (neither like/nor dislike) out of 7, indicating the supplement was well-liked for the duration of supplementation, and was never disliked.

Table 3-2. Reported daily nutritional supplement intake for all study participants (n = 12) over the 7-day the supplementation period.
(Mean values and standard deviations)

	Mean	SD
g/d	273	38
kcal/d	640	89
g protein/d	33	5
g EPA/d	0.91	0.13
g DHA/d	0.74	0.10

3.3.3 Change in Total and Meal Derived Calorie and Protein Intakes for All Study Participants

Considering the overall response to the supplement (n=12), there was an increase ($P<0.01$) in total (meal + supplement) energy (414 SD 462 kcal/d) and protein (30 SD 14 g protein/d) intakes when compared to baseline. Therefore, supplementation increased ($P<0.01$) energy and protein intakes to 40 kcal/kg BW/d and 1.7 g/kg BW/d respectively, and the contribution of protein to total energy intake increased ($P=0.004$) from 14% to 17%. There was no change ($P>0.05$) in meal derived energy (-209 SD 481 kcal/d) and protein (-3 SD 13 g protein/d) intakes during supplementation. There was no difference ($P>0.05$) between protein intakes estimated from diet records and UUN excretion at

baseline or during supplementation indicating diet records were recorded accurately (Figure 3-1).

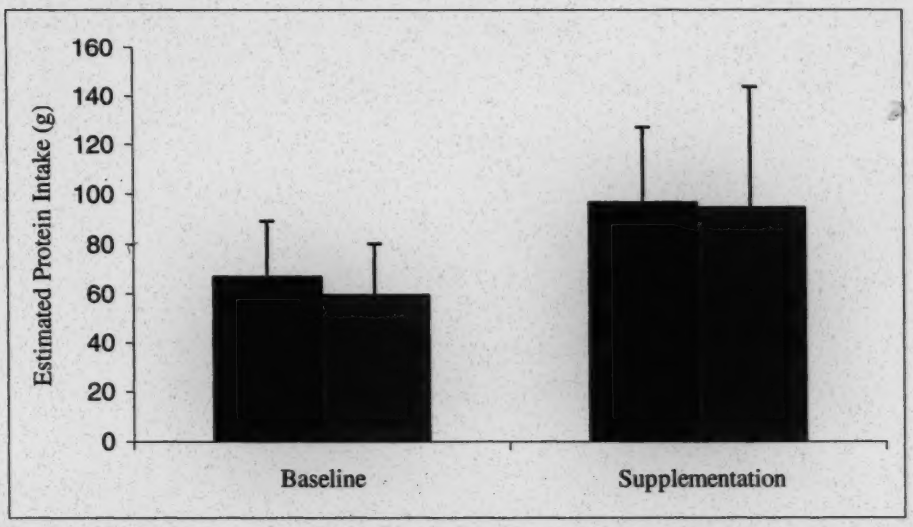

Figure 3-1. Estimated protein intake at baseline and during the supplementation period (n=12). Protein intake estimated from diet records (■), and from 24-hour urinary urea nitrogen (UUN) excretion (■). Values are means with standard deviations shown by vertical bars. Mean protein intakes estimated from UUN excretion were not statistically different, P>0.05, from mean protein intakes estimated from diet records using student's t-test for unpaired data, two-tailed.

3.3.4 Change in Total and Meal Derived Calorie and Protein Intakes for Compensators and Non-compensators

There were clearly two distinct behavioral responses to the supplement: patients who reduced their meal derived energy intake (*compensators*) and those whose meal derived energy intakes did not change (*non-compensators*) (Figure 3-2, Table 3-3). Baseline energy and protein intakes were not different (P>0.05) between the 2 groups. Compensators (n=6) reduced (P=0.015) their meal derived energy intakes such that there was no increase in total (meal + supplement) energy

intakes when compared to baseline (Figure 3-2, Table 3-3). However, these patients increased (P=0.001) their protein intakes (Figure 3-3). Protein intakes were increased to 1.4 g/kg BW/d. Non-compensators (n=6) had no change in meal derived energy intakes during supplementation (Figure 3-2, Table 3-3). Non-compensators showed robust increases (P<0.01) in total energy and protein intakes compared to baseline (Figure 3-2, Figure 3-3). Energy and protein intakes increased to 37 kcal/kg BW/d and 2.0 g/kg BW/d respectively. Age, height, weight, BMI, % weight loss in the past 6 months, and data reported from the PG-SGA, ESAS, and taste and smell questionnaires were not different (P>0.05) between the two groups. However, compensators had a higher incidence of self-reported early satiety (nutrition impact symptom from PG-SGA) than did the non-compensators (4/6 versus 2/6 patients).

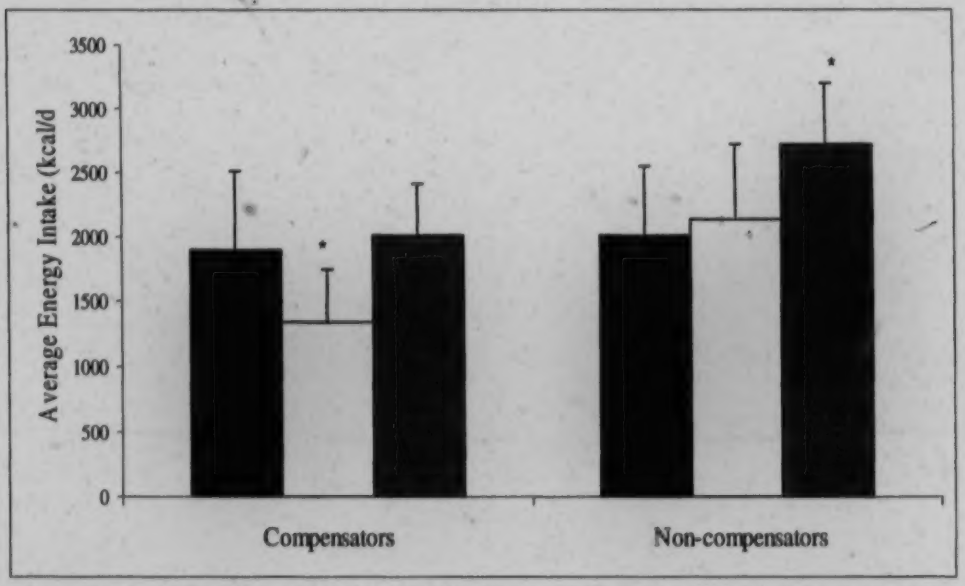

Figure 3-2. Average energy intake at baseline (■), meal energy intake during the supplementation period (□), and total (meal + supplement) energy intake during the supplementation period (■). Values are means with standard deviations shown by vertical bars. Mean values were significantly different, * $P<0.05$, when compared to baseline energy intakes using student's paired t-tests, two-tailed.

Table 3-3. Change in total intakes (meal + supplement) and meal intakes with inclusion of a nutritional supplement for compensators and non-compensators. (Mean values and standards deviations)

	Mean	SD	p-value
Change in Total Intake			
Compensators (n = 6)			
kcal/d	111*	372	0.50
kcal/kg BW/d	2	6	0.59
g protein/d	24*	12	0.005
g protein/kg BW/d	0.4	0.2	0.005
Non-compensators (n = 6)			
kcal/d	717	331	0.003
kcal/kg BW/d	12	7	0.007
g protein/d	36	13	0.001
g protein/kg BW/d	0.6	0.2	0.000
Change in Meal Intake			
Compensators (n = 6)			
kcal/d	-551*	368	0.015
kcal/kg BW/d	-9	7	0.02
g protein/d	-11*	12	0.06
g protein/kg BW/d	-0.2	0.2	0.08
Non-compensators (n = 6)			
kcal/d	134	302	0.33
kcal/kg BW/d	2	0.7	0.31
g protein/d	5	8	0.19
g protein/kg BW/d	0.1	0.1	0.22

Means are presented as the absolute change in calorie and protein intakes (intake during supplementation – intake at baseline).
Mean values were statistically significant, $P < 0.05$, from baseline using paired student's t-tests, two tailed.
* $P < 0.05$ when compensators were compared to non-compensators.

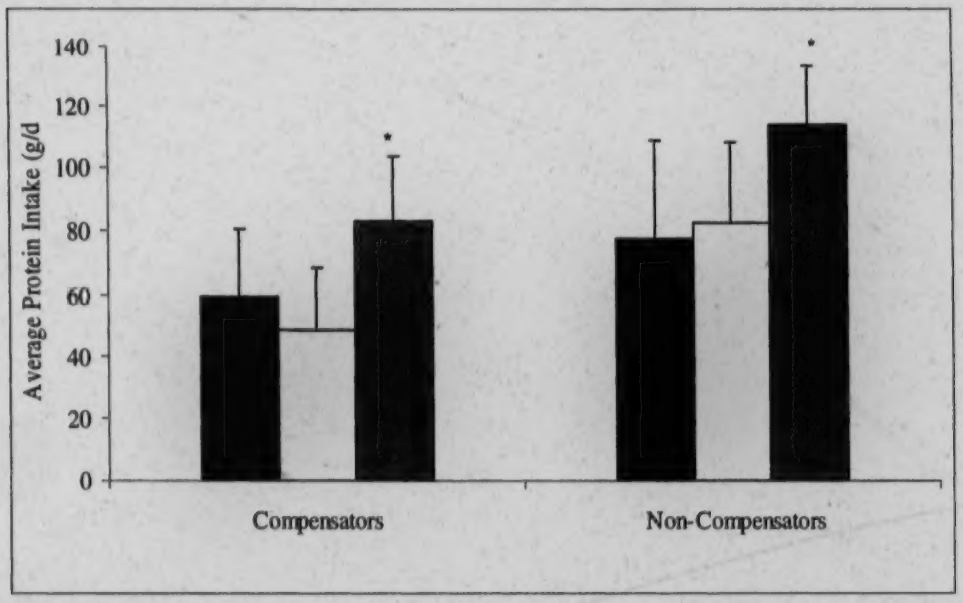

Figure 3-3. Average protein intake at baseline (■), meal protein intake during the supplementation period (□), and total (meal + supplement) protein intake during the supplementation period (■). Values are means with standard deviations shown by vertical bars. Mean values were significantly different, * $P < 0.05$, from baseline energy intakes using student's paired t-tests, two-tailed.

3.3.5 Plasma Phospholipid EPA and DHA Levels

There was an increase ($P=0.04$) in saturated fatty acids, no change ($P>0.05$) in plasma total PL, 20 : 5*n*-3, or 22 : 6*n*-3, and a decrease ($P<0.05$) in PUFA, total *n*-6 fatty acids and 20 : 4*n*-6 after 7 days of supplementation (Table 3-4). Results were similar for compensators and non-compensators (data not shown).

Table 3-4. The effect of supplementation on the fatty acid composition (% (w/w) total fatty acids) of total plasma phospholipids (n=12).
(Mean values and standards deviations)

	Baseline		Post-supplementation		
	Mean	SD	Mean	SD	P-value
∑ SFA	43.4	1.5	46.2	3.0	0.04
∑ MUFA	16.8	1.3	16.2	2.9	0.47
∑ PUFA	39.8	2.0	37.3	3.5	0.04
∑ n-6	31.3	4.0	28.0	2.6	0.04
20 : 4*n*-6	9.9	1.2	9.1	0.8	0.05
∑ n-3	9.1	4.3	9.3	3.6	0.84
20 : 5*n*-3	3.1	3.0	4.0	2.3	0.37
22 : 6*n*-3	5.2	1.8	5.1	1.7	0.86
n-6 to n-3 ratio	4.9	3.1	3.7	2.2	0.32
μg plasma PL	918.0	214.4	883.5	264.1	0.72

Mean post-supplementation values when compared to baseline were statistically significant, $P<0.05$, using paired student's t-tests, two tailed.

3.4 Discussion

This small and simply designed investigation reveals a key nutritional issue related to dietary supplementation in patients with advanced malignant disease. This population includes distinct subsets of individuals, who behave in entirely opposite fashions in response to a dietary supplement. One subset would appear to regulate energy intake relatively precisely but unfortunately at a low level, such that 87% of the supplement energy was involuntarily deleted from other meals of the day. This behavior (compensation) almost entirely defeated the objective of increasing total caloric intake through supplementation. A second, distinct subset increased total energy intake robustly during supplementation.

It is important to note the methodological questions surrounding self-reported dietary intakes. A commonly reported concern is that energy intakes have been underreported in normal weight, obese, and elderly individuals (Livingstone, 1995; Buzzard, 1998; Hill & Davies, 2001). Here we noted very good correspondence between self-reported intakes and actual intakes based on urinary urea nitrogen; Bruera et al. (1986) also found good correlation between the 24-hour food records of advanced cancer patients, and their actual energy and protein intakes. Collecting dietary intakes for seven days is the preferred method, however, three day diet records have been reported to be highly correlated with seven day food records (Stuff et al., 1983; Jackson et al., 1986; Fruedenheim et al., 1987), and Gersovitz et al. (1978) found in the elderly, that food records collected for more than 3 days were less accurate. Therefore, a 3 day collection period is an acceptable compromise between the extensiveness of the record and the age and relative vulnerability of advanced cancer patients.

Fearon et al. (2003) reported the dietary intakes of pancreatic cancer patients during supplementation for up to 8 weeks. Patients on the control arm (n=56) consumed a standard, commercially available enteral supplement. While it was not the objective of this study to follow up individual behaviors, the aggregate data presented indicated on average these patients reduced their meal energy intakes by an amount equal to 85% of supplement energy intake, a value similar to that obtained here. The success of nutritional supplements depends on sufficient quantities being consumed over time (Van der Schueren, 2005). If compensation of ~85% is indeed a generality in patients with advanced malignant

disease, it would provide a plausible explanation as to why nutritional supplementation has frequently been reported to fail at improving outcomes such as weight, lean tissue and functional status (Stratton & Elia, 1999). Nutritional intervention studies rarely include documentation of compliance, and results presenting compensating reductions in meal intakes suggest such studies can only be meaningfully interpreted when the effects of supplementation on habitual meal intakes are also recorded. The implications of reductions in meal intake are nutritionally important. The *compensators* defend total intakes around a value that maintains negative energy balance. Therefore, supplementation is largely ineffective, especially in the case that the nutritional product employed does not have a different overall nutrient composition than the diet it replaces.

Our nutritional supplement was developed with care and attention to the patient population in question, and this was rewarded with very high compliance in the short-term. Whether this degree of compliance would be borne out over the long term remains to be established, however it should be noted it appears possible to create highly palatable food items for this patient group. Our nutritional supplement had a higher protein content than the usual diet of the patients we studied (21% versus 14% of energy). The nutritional supplement thus increased protein intakes to ~1.7 g/kg BW/d for all study participants, and increased the protein content of the diet overall to ~17% of energy. Additionally, the *n-3* fatty acid content of the nutritional supplement had effects on the fatty acid composition of plasma PL. Although there were no change to 20:5*n*-3 and 22:6*n*-3, there were significant reductions in 20 : 4*n*-6, similar to previous results

obtained in advanced cancer patients (Pratt et al., 2002). Compared to previous studies of *n-3* fatty acid supplementation (Wigmore et al., 1996; Pratt et al., 2002; Fearon et al., 2003; Bauer & Capra, 2005), we used a shorter intervention period (7 days compared to 2-12 weeks), and a supplement with a lower EPA and DHA content (1.7 g/d compared to >3 g). However, levels of EPA and DHA would be expected to increase further with time. Smaller doses of EPA and/or DHA (e.g. 100 to 150 mg/d of DHA only; 1.35 g EPA + 0.3 g DHA/d) have been reported to increase DHA and/or EPA in plasma PL after 3 months of supplementation (Payet et al., 2004; Rees et al., 2006).

According to Rolls et al. (1995) "the major challenge to understanding the regulation of food intake is to determine what characteristics of individuals affect the ability to show compensation". It will be important to differentiate individuals who experience compensatory behaviors and those who do not. It may be that these differences are quantifiable and measurable in terms of peripheral signals related to appetite and satiety, and elements of gastrointestinal physiology (Wilson & Morley, 2003). For example, prolonged gastric emptying rates have been reported in advanced cancer patients (Shivshanker et al., 1983; Bruera et al., 1987; Nelson et al., 1993) and these are known to suppress food intake in the short term (Hunt 1980). Until it becomes possible to differentiate patients who will compensate, the nutritional supplementation of cancer patients will continue to be burdened by very low overall efficacy, and will ultimately be unsuccessful in certain individuals.

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CHAPTER 4

4.1 SUMMARY

Malnutrition is prevalent in patients with advanced cancer, and is associated with reduced quality of life and survival (Vigano et al., 2000; MacDonald et al., 2003). Existing practices and therapeutic interventions targeting the malnutrition of advanced cancer patients focus on improving appetite using drug therapies, and/or improving dietary intakes with nutritional supplements. In clinical nutrition practice, oral liquid or powdered supplements are considered a convenient way to improve dietary intakes, and are often recommended with the intention of preventing further weight loss and/or encouraging weight gain.

Unfortunately, nutritional supplementation has failed to improve weight, body composition, and functional status among cancer patients (Stratton & Elia, 1999; Elia et al., 2006). Reasons for the lack of successful outcomes are not well understood. One study examined the dietary intakes and habits among patients with advanced cancer (Hutton et al., 2006). Results from this work described advanced cancer patients as a heterogeneous group with regard to their dietary intakes and food selection. Additionally, these patients had a wide variation in their energy intakes with ~ 83% of individuals falling below the recommended energy requirements (30 to 35 kcal/kg BW/day) for weight maintenance. The authors suggested attempts to improve energy intakes through pharmacologic and nutritional therapies would not induce weight gain among individuals with the lowest intakes, unless they were capable of doubling or even tripling their current

dietary intakes to meet recommended levels. As well, although nutritional supplements are a popular recommendation, they are not selected by ~ 70% of cancer patients (Brown & Radke, 1998; Thoreson et al. 2002; Hutton et al., 2006). Therefore, other forms of nutritional supplementation should be explored, such as augmenting the nutrient composition of foods that are habitually consumed. This recommendation laid the foundation for the current research project.

4.2 Issues Related to Nutritional Supplementation

Several issues must be considered in order for nutritional supplementation to be successful. First, there are multiple symptomatic barriers to oral intake including anorexia, pain, nausea, constipation, xerostomia, and dysphagia (Donnelly & Walsh, 1995; Walsh et al., 2000), with pain and nausea being described as the main impediments to food intake (Shragge, 2006). As well, a recent review by Davis et al. (2006) identified early satiety as one of the main determinants of reduced dietary intakes. Occurrence of these symptoms makes it exceedingly difficult to maintain adequate dietary intakes to meet the recommendations for weight maintenance. However, despite the presence of one or more of these symptoms, advanced cancer patients are capable of maintaining some degree of oral intake (Fuez et al., 1994; Orrevall et al., 2004; Shragge, 2006). Therefore, careful control over these symptoms may help to improve dietary intakes (Orrevall et al., 2004).

In addition to adequate symptom management, several pharmacological agents have been investigated for improving appetite in cancer patients. To date

only two drugs have adequate evidence to support their use for appetite loss – progestins and corticosteroids. Progestins have demonstrated beneficial effects on appetite, caloric intake, weight gain, and sense of well being (Bruera & Gagnon, 1998; Yavuzsen et al., 2006). However, this class of drug is only effective in subsets of individuals, and weight gain is generally seen as an increase in adipose tissue (Bruera & Gagnon, 1998; Yavuzsen et al., 2005). Corticosteroids have also demonstrated improvements in appetite, food intake, and well-being (Breura & Gagnon, 1998; Yavuzsen et al., 2005). Unfortunately, the beneficial effects are short lasting (2 to 8 weeks) and use of these drugs has been suggested for patients with short expected survival (Bruera & Gagnon, 1998; Yavuzsen et al., 2005). Despite their shortcomings these drugs are considered effective treatments for appetite loss however, it is unlikely their use alone would drastically improve dietary intakes to meet the recommendations for weight maintenance unless food and/or nutritional products selected are consumed in sufficient quantities to be able to support the energy and protein requirements of these individuals.

Therefore, another important component for successful nutritional supplementation includes the selection of nutrient dense food and nutritional products for consumption. Palatability plays an important role in determining the type of food selected and the amount of food that will be consumed. The next step is to sustain supplement consumption, which is a challenge in individuals with reduced dietary intakes. Unfortunately, palatability does not dictate compliance to nutritional prescriptions. Despite good initial (short-term) compliance to a nutritional prescription declining compliance over the long term has been

observed (Bolton et al., 1990; Fearon et al., 2003; Ravasco et al., 2005a). This decline occurs regardless of good initial product acceptance, and is typically the result of taste fatigue and lack of flavor variety (Ravasco, 2005b). Additionally, the decrease in preference for a product over time is more likely to occur with non-staple foods upon repeated exposures, whereas staple foods are less likely to give rise to decreases in liking over time (Weenen et al., 2005). Results from the present work demonstrated that it is possible to develop a palatable nutritional product that is well liked and will be consumed over the short-term. However, determining compliance over the long term remains to be determined. It is more likely for supplement consumption to be sustainable with the provision of a variety of palatable, habitually consumed food items and/or nutritional products.

Unfortunately, it would be counterproductive to attempt to improve appetite and dietary intakes without first addressing the individuals' ability to physiologically process the food they ingest. Results from the present study illustrate this point, despite high compliance to the nutritional prescription a subset of individuals exhibited compensating behaviors such that their total energy intakes did not change. Early satiety may be a possible explanation for the results observed here. According to Davis et al. (2006), early satiety is thought to have both central and peripheral etiologies; central factors associated with early satiety may include taste and smell changes, food aversions, and diurnal variations in food intake; peripheral factors may include delayed gastric emptying, lack of gastric capacity, and altered enteric neuron sensory signals.

Therefore, it would appear the management of early satiety requires a two pronged approach. Management of central factors involved in early satiety could include providing a variety of palatable food items and nutritional products to overcome satiation caused by unpleasant foods and food aversions. Management of peripheral factors involved in early satiety could include pharmacologic therapies for delayed gastric emptying and reduced gastric capacity. Prokinetic agents are often used to manage delayed gastric emptying however, many patients fail to respond to these drugs or develop side effects (Davis et al., 2006). Although it has been suggested those who fail to respond to prokinetic agents may have reduced gastric capacity, which may be treated with vasodilators (Davis et al., 2006).

Unfortunately, early satiety is an often underrecognized symptom of advanced cancer, and more research is required to understand how to properly manage this symptom. If the inability to effectively increase dietary intakes in certain individuals i.e. if compensating behaviors are related to early satiety then it would be important to effectively treat this symptom before attempting to increase dietary intakes using appetite stimulating medications, and energy and protein dense foods and/or nutritional products. Attempting to improve dietary intakes without first identifying and treating early satiety may result in the very symptoms that impede food intake such as nausea and pain.

4.3 The Role of Nutrition in Advanced Cancer

The role of nutritional supplementation in advanced cancer patients has not been clearly defined in the scientific literature (Arends et al., 2006). Therefore, recommending nutritional supplements for all individuals, without first identifying individuals for which supplements have the potential to be ineffective would appear to be irresponsible – adding extra financial costs, and because of the possibility of meal displacement, reduced enjoyment and socialization at meal times. The latter is an important and often overlooked consideration. Mealtimes are an important way of expressing and maintaining relationships between individuals (Orrevall et al., 2004). Although nutritional status remains an important aspect in the care of advanced cancer patients, blanket recommendations to increase dietary intakes using nutritional supplements may not be the best solution. The issues surrounding nutritional supplementation are complex. Food and the eating process are large components of peoples' daily lives, and when foods' enjoyment and ability to nourish are reduced it becomes distressing to patients and their families. Continued focus on the need to eat more calories and protein, the extra effort required to include nutritional supplements into dietary patterns, and the inability to attain recommended intakes for weight gain lead to feelings of disappointment and anxiety, which have a negative emotional impact on patients and their families (Orrevall et al., 2004; Shragge, 2006). Because much of what the advanced cancer patient experiences throughout the course of their disease is specific to the individual, i.e. their nutritional preferences, the type of chemosensory alterations and symptoms experienced, and

the degree of social support, nutrition advice should attempt to meet patients and their families where they are in terms of their nutritional status and current dietary pattern.

Providing the appropriate pharmacological interventions to maintain adequate symptom control, and educating patients and their families how to improve their diet quality and framing these recommendations within their current dietary patterns may be beneficial in terms of encouraging and sustaining food intake. Recent studies suggest individualized dietary counseling based on regular foods is the most effective means of improving nutritional intake, status, and quality of life in patients undergoing radiotherapy (Isenring et al., 2004; Ravasco et al., 2005a). As well, it has been demonstrated that food acceptance in cancer patients is improved with the provision of foods that are aligned with current food preferences and eating habits (Fuez et al., 1994; Pettey et al. 1998). Dietary counseling may be useful in the management of nutrition impact symptoms, and for correcting or improving the quality of dietary patterns known to be of low nutrient value. As well, explaining the stages of appetite loss and other eating changes expected during the course of cancer may help reduce tension and lessen the emotional impact of appetite loss and reduced dietary intakes on patients and their family members (Shragge, 2006).

4.4 Final Comments

The results presented in this body of work have identified compensating behaviors as an important challenge to the successful implementation of

nutritional supplements. This behavior may be the manifestation of early satiety. Therefore, improving dietary intakes should focus on all possible factors that have a negative impact an individual's ability to eat. All aspects related to the eating process must be considered i.e. the symptoms that prevent one from ingesting food e.g. pain, nausea, taste and smell alterations, and food aversions, as well as the symptoms that limit the amount one can eat e.g. early satiety. Overall, the results presented here are thought provoking and lend further support to the requirement for improved identification and management of nutrition impact symptoms, in particular early satiety. These findings require further exploration before it would be possible to suggest changes to current clinical practice guidelines. Nevertheless, the results can be used to encourage nutrition professionals to re-examine the type of nutrition recommendations made in clinical practice and to promote awareness of potential problems associated with nutritional supplementation. Because the role of nutritional supplementation in advanced cancer patients has not been clearly defined, nutrition professionals should focus on individualized dietary counseling versus generalized recommendations for increased energy and protein intakes. This type of patient care may be more beneficial in terms of managing dietary intakes and maintaining quality of life because it would allow patients and their families to work within their current dietary habits and preferences. Additional good quality research is required to effectively examine the role of nutrition along with pharmacological therapies in the management of symptoms know to affect dietary intakes.

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APPENDIX A

INFORMATION SHEET

Consumer Taste Testing of a Custard Designed for Cancer Patients

You will be asked to evaluate your liking of a sample of custard that has been designed specifically for cancer patients. In addition, you are asked basic information about your senses of **taste** and **smell**. There are no right or wrong answers to the evaluation; it is your opinion that is important. The evaluation should take no more than 15 minutes. The custard has been designed to provide extra energy, protein, and essential fatty acids to improve nutrient intake in cancer patients.

Please read the list of ingredients.

List of Ingredients:

1. Liquid egg product (liquid egg white, liquid yolk, lecithin, citric acid, beta carotene, egg flavour, guar gum, xanthan gum, arabic gum, salt)
2. Homogenized milk
3. White granulated sugar
4. Powdered egg white
5. Essential fatty acids (eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA) with gelatin, sodium polyphosphate, sodium ascorbate, soybean and/or canola oil, natural flavours, tocopherols, citric acid)
6. Natural and/or artificial flavours (vanilla)

If you have any **ALLERGIES, INTOLERENCES, SENSITIVITIES**, and/or **FOOD AVERSIONS** to any of the ingredients listed you may **NOT** participate.

This taste test is part of a research project. The focus of this research is to help cancer patients meet their nutritional requirements. Your custard evaluation will be averaged with information from the other participants to provide us with direction about how we can improve the custard.

Your participation is voluntary and confidential; we do not need to know your name. You can stop your evaluation at any time.

APPENDIX B

EVALUATION OF VANILLA CUSTARD DESIGNED FOR CANCER PATIENTS

The purpose of this survey is to gather information about your senses of **TASTE** and **SMELL** and to assess your **acceptance of a nutrient – rich custard designed specifically for cancer patients**. Please answer the following questions the best you can.

PART A – TASTE AND SMELL

1. Are you currently receiving chemotherapy or radiation to the head and/or neck?
YES **NO**

If **NO**, when was your last treatment? _____

2. Have you noticed any changes in your sense of **SMELL** since you were diagnosed with cancer? **YES** **NO**

3. Have you noticed any changes in your sense of **TASTE** since you were diagnosed with cancer? **YES** **NO**

4. Compare your sense of **TASTE** now to the way it was before you were diagnosed with cancer (place a mark the box that BEST describes your sense of taste):

	Stronger	As Strong	Weaker	I Cannot Taste At All
1. **SALT**				
2. **SWEET** (e.g. sugar)				
3. **SOUR** (e.g. lemon or vinegar)				
4. **BITTER** (e.g. black coffee or tonic water)				

PART B – CUSTARD EVALUATION

Place a mark in the box that **BEST** describes how you feel about the custard.

1. How **SWEET** is the custard?

☐ ☐ ☐ ☐ ☐ ☐ ☐

Not Sweet At All — Just About Right — Much Too Sweet

2. How **STRONG** is the vanilla flavor of the custard?

☐ ☐ ☐ ☐ ☐ ☐ ☐

Not Strong At All — Just About Right — Much Too Strong

3. The **CONSISTENCY** of the custard is

☐ ☐ ☐ ☐ ☐ ☐ ☐

Much Too Thin — Just About Right — Much Too Thick

4. The **PORTION SIZE** of the custard as a snack is:

☐ ☐ ☐ ☐ ☐ ☐ ☐

Much Too Small — Just About Right — Much Too Big

5. Overall, how much do you **LIKE** this product?

☐ ☐ ☐ ☐ ☐ ☐ ☐

Dislike Extremely — Neither Like/ Nor Dislike — Like Extremely

6. Please add any additional comments you may have about the custard.

_____

7. Do you think you could eat 2 portions of this custard everyday for a week?
   YES **NO**

APPENDIX C

Patient-Generated Subjective Global Assessment

History (Boxes 1-4 are designed to be completed by the patient)

1. Weight

In summary of my current and recent weight:

My is height about _____ feet / inches tall
(or _____ cm)

My current weight is about _____ pounds
(or _____ kg)

One month ago I weighed about _____ pounds
(or _____ kg)

Six months ago I weighed about _____ pounds
(or _____ kg)

During the past two weeks my weight has:

- ☐ decreased
- ☐ not changed
- ☐ increased

2. Food Intake:

As compared to my normal intake, I would rate the QUANTITY of my food intake during the past month as:

- ☐ unchanged
- ☐ more than usual
- ☐ less than usual

I am now taking food of the following TYPE:

- ☐ *normal food* but less than normal amount
- ☐ little solid food
- ☐ only liquids
- ☐ only nutritional supplements
- ☐ very little of anything
- ☐ only tube feedings or only nutrition by vein

3. Symptoms: I have had the following problems that have kept me from eating enough during the past two weeks (check all that apply):

- ☐ no problems eating
- ☐ no appetite, just did not feel like eating
- ☐ nausea ☐ vomiting
- ☐ constipation ☐ diarrhea
- ☐ mouth sores ☐ dry mouth
- ☐ things taste funny or have no taste
- ☐ smells bother me
- ☐ problems swallowing
- ☐ dental problems
- ☐ feel full quickly
- ☐ pain; where? _____
- ☐ other* _____

* Example: depression, money

4. Activities and Function: Over the past month, I would generally rate my ACTIVITY as:

- ☐ normal with no limitations
- ☐ not my normal self, but able to be up and about with fairly normal activities
- ☐ not feeling up to most things, but in bed or chair less than half the day
- ☐ able to do little activity and spend most of the day in bed or chair
- ☐ pretty much bedridden, rarely out of bed

Information Provided by : ☐ Patient ☐ Family Member

Signature:_____ **Date:** _____

APPENDIX D

TASTE AND SMELL PERCEPTION IN CANCER PATIENTS

The purpose of this survey is to see how cancer affects the senses of taste and smell.
Please answer the following questions as best you can.

Participant Number:_____ Date:_____

1. Have you noticed any changes in your sense of taste? yes no

   If yes, please describe:_____

   _____

2. Have you noticed any changes in your sense of smell: yes no

   If yes, please describe:_____

3. Have you ever noticed that a food tastes different than it used to? yes no

   If yes, please describe:_____

4. Have you ever noticed that a food smells different than it used to? yes no

   If yes, please describe:_____

5. I have a persistent bad taste in my mouth (circle **BEST** answer)

   1. never
   2. rarely
   3. sometimes
   4. often
   5. always

6. The persistent bad taste is (circle **ALL** that apply)

   1. salty
   2. sweet (like sugar)
   3. sour (like lemon or vinegar)
   4. bitter (like black coffee or tonic water)
   5. other (please specify):_____

7. Do specific drugs interfere with your sense of taste? yes no

If yes, which ones?_____

8. Do some drugs taste worse than others? yes no

If yes, which ones?_____

9. Do specific drugs interfere with your sense of smell? yes no

If yes, which ones?_____

10. Do some drugs smell worse than others? yes no

If yes, which ones?_____

11. Comparing my sense of taste now to the way it was before I was diagnosed with cancer:

a. Salt tastes (circle **BEST** answer)

1) stronger
2) as strong
3) weaker
4) I cannot taste it at all

b. Sweet (sugar) tastes (circle **BEST** answer)

1) stronger
2) as strong
3) weaker
4) I cannot taste it at all

c. Sour (lemon) tastes (circle **BEST** answer)

1) stronger
2) as strong
3) weaker
4) I cannot taste it at all

d. Bitter (black coffee or tonic water) tastes (circle **BEST** answer)

1) stronger
2) as strong
3) weaker
4) I cannot taste it at all

12. Comparing my sense of smell to the way it was before I was diagnosed with cancer, odors are

1) stronger
2) as strong
3) weaker
4) I cannot smell at all

13. Over the past 3 months, I would rate my abnormal sense of taste as: (circle **BEST** answer)

1) insignificant
2) mild
3) moderate
4) severe
5) incapacitating

14. How has your abnormal sense of taste affected your quality of life?

_____

15. Over the past 3 months, I would rate my abnormal sense of smell as: (circle **BEST** answer)

1) insignificant
2) mild
3) moderate
4) severe
5) incapacitating

16. How has your abnormal sense of smell affected your quality of life?

_____

APPENDIX E

ESAS

Please Circle the Number that Best Describes:

No Pain	0	1	2	3	4	5	6	7	8	9	10	Worst Possible Pain
Not Tired	0	1	2	3	4	5	6	7	8	9	10	Worst Possible Tiredness
Not Nauseated	0	1	2	3	4	5	6	7	8	9	10	Worst Possible Nausea
Not Depressed	0	1	2	3	4	5	6	7	8	9	10	Worst Possible Depression
Not Anxious	0	1	2	3	4	5	6	7	8	9	10	Worst Possible Anxiety
Not Drowsy	0	1	2	3	4	5	6	7	8	9	10	Worst Possible Drowsiness
Best Appetite	0	1	2	3	4	5	6	7	8	9	10	Worst Possible Appetite
Best Feeling of Wellbeing	0	1	2	3	4	5	6	7	8	9	10	Worst Possible Feeling of Wellbeing
No Shortness of Breath	0	1	2	3	4	5	6	7	8	9	10	Worst Possible Shortness of Breath

APPENDIX F

RECORD OF SUPPLEMENT CONSUMPTION AND ACCEPTANCE

DAY:_____ PORTION:_____

DATE: _____

Time supplement consumed: _____

1. How much of the custard supplement did you eat? (Choose the answer that best applies)

Ate None 0%

Ate a Little 25%

Ate Half 50%

Ate a Lot 75%

Ate All 100%

2. How much did you like the custard supplement?

☐ ☐ ☐ ☐ ☐ ☐ ☐

Dislike Extremely

Neither Like/ Nor Dislike

Like Extremely